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Journal of the American College of Cardiology Vol. 47, No. 9, 2006
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Published by Elsevier Inc.

ISSN 0735-1097/06/$32.00

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Early Versus Delayed Enalapril in Patients With Left Ventricular Systolic Dysfunction: Impact on Morbidity and Mortality 15 Years After the SOLVD Trial

To the Editor: The Studies Of Left Ventricular Dysfunction (SOLVD) trial showed that enalapril, an angiotensin-converting enzyme (ACE) inhibitor, reduced morbidity and mortality in patients with ejection fractions ≤35% (1,2), including the risks of myocardial infarction and unstable angina (3). Recently, the Extended SOLVD (X-SOLVD) trial indicated that the mortality benefit continued to accrue for a decade beyond the original trial period (4). In this longest follow-up of any heart failure randomized clinical trial, we compared the 15-year post-trial mortality and serious cardiovascular (CV) morbidity among patients who were initially randomized to either enalapril or placebo, offering an opportunity to assess the clinical consequences of delaying the initiation of ACE inhibitor therapy.

The initial study cohort consisted of all 558 Belgian patients among the 6,797 subjects enrolled in the prevention and treatment arms of the SOLVD trial. At trial close-out, 433 patients (97 in treatment and 336 in prevention arms) were still alive (218 in enalapril and 215 in placebo groups) and received open-label enalapril therapy (Table 1). Post-trial morbidity and mortality status was established by direct or telephone contact with patients, relatives, or physicians involved in their care and through reviews of the patients' medical records. Each patient gave informed consent, and the study protocol was approved by the local institutional review board. The primary end point was the composite outcome of death or serious CV morbid events, defined as development of heart failure, myocardial infarction, or stroke, or need for heart transplant, device therapy (pacemaker, implantable cardioverter-defibrillator), or myocardial revascularization (coronary angioplasty, bypass surgery). Causes of death, available for all subjects, were classified using the International Classification of Diseases-Ninth Revision (ICD-9) code. Morbidity data were only available for subjects still alive at last contact.

Table 1. Baseline Characteristics of Patients in Post-Trial Follow-Up According to Randomized Drug Therapy

Characteristics	Enalapril (n = 218)	Placebo (n = 215)	p
Age* (yrs)	60	61	0.20
Ejection fraction* (%)	29	29	0.58
Trial arm			0.34
Prevention	165 (76%)	171 (80%)	
Treatment	53	44	
Gender			0.37
Male	183 (84%)	187 (87%)	
Female	35	28	
NYHA functional class			0.18
I	81 (37%)	78 (36%)	
II	105 (48%)	117 (54%)	
III–IV	32	20	
Etiology			0.22
Ischemic	167 (77%)	175 (81%)	
Others	51	40	
Prior hypertension			0.59
Yes	45 (21%)	40 (19%)	
No	173	175	
Prior diabetes mellitus			0.38
Yes	17 (8%)	22 (10%)	
No	201	193	

*Median values.
NYHA = New York Heart Association.

Statistical analysis was performed on an intention-to-treat basis according to the drug therapy assigned at the time of randomization in the SOLVD trial. The composite outcome was defined hierarchically based on the most serious adverse event. Among subjects who had died during the extended follow-up, death was recorded as the most serious adverse outcome event. In comparison, among subjects who were still alive at last contact, the first morbid event was recorded as the most serious adverse outcome event. Time-to-event curves for morbidity and mortality during the extended follow-up were compared between enalapril and placebo groups using the generalized Wilcoxon test. Hazard ratios were calculated based on Cox regression models. The Breslow-Day test was used to assess for homogeneity of treatment effect from early enalapril therapy across the two arms of the SOLVD trial.

The median duration of follow-up was 15.5 years from randomization and 12.2 years from study close-out. No patients were lost to follow-up. Among the 131 subjects who were alive and had not undergone heart transplantation at last contact, no difference was observed in the proportion taking ACE inhibitors after the trial between the enalapril and placebo groups (85% vs. 79%, p = 0.40).

Fewer deaths (138 vs. 150) occurred among patients treated early with enalapril as compared with placebo (63% vs. 70%, Wilcoxon p = 0.01) (Fig. 1), corresponding to a 6.5% absolute risk reduction in mortality. This benefit was apparent within the first year after trial close-out and persisted for the entire duration of follow-up. The combined risk of death or serious CV morbid event during the extended follow-up was significantly lower in enalapril (177 of 218 [81%]) than in placebo patients (188 of 215 [87%]) (Wilcoxon p = 0.008), corresponding to a 6.2% absolute risk reduction in favor of early enalapril therapy. The benefits of early enalapril therapy were similar between patients enrolled in the prevention and the treatment arm of the SOLVD trial (tests of homogeneity, p = 0.73 for death and p = 0.39 for combined death or serious CV morbid event).

Among patients still alive at follow-up, early enalapril therapy was associated with a 14% absolute reduction (10 of 80 [12%] vs. 17 of 65 [26%]; Wilcoxon p = 0.04) and a 57% relative reduction in nonfatal cardiac ischemic events, as defined by the occurrence of myocardial infarction or the need for coronary angioplasty or bypass surgery (hazard ratio 0.43, 95% CI 0.20 to 0.95, p = 0.04). Our data also showed that the risk of death or nonfatal cardiac ischemic events was significantly lower among patients who received enalapril early as in-trial therapy than among those who only received enalapril after the trial ended (148 of 218 [68%] vs. 167 of 215 [78%]; Wilcoxon p = 0.001).

Excluding heart transplantations, 61 patients remained free of any adverse CV event during the extended follow-up, as compared

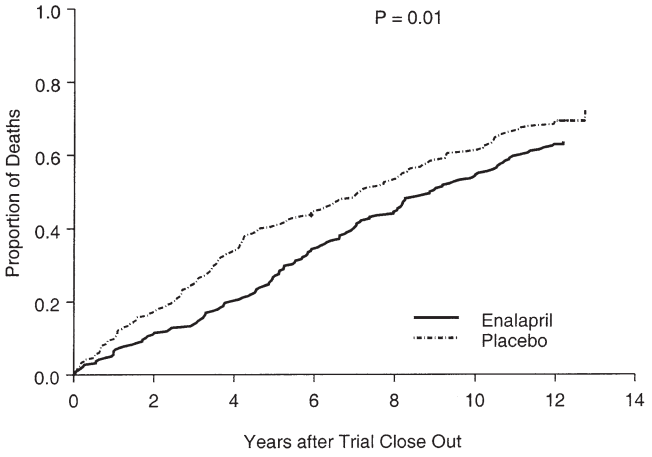

Figure 1. Kaplan-Meier mortality curves during the post-trial period between patients randomized to enalapril and to placebo. The data showed that the benefit in the enalapril group was apparent within the first year after trial close-out and persisted for the entire duration of the extended follow-up (Wilcoxon p = 0.01).

with 358 who had at least one adverse event. Considering the baseline characteristics, event-free patients were younger (54 vs. 61 years, p = 0.0001), had a lower functional class (New York Heart Association functional class I to II 97% vs. 87%, p = 0.003), and had a higher ejection fraction (32% vs. 29%, p = 0.002) at randomization. Event-free patients were also more likely to receive in-trial enalapril therapy than placebo (38 [62%] vs. 173 [48%], p = 0.04).

Our data indicated that early enalapril therapy reduced death and serious CV morbid events at 15 years in the Belgian SOLVD cohort. Specifically, at the end of this extended follow-up, a significant risk reduction in mortality was observed among patients treated early with enalapril compared with placebo, confirming our previous findings in the X-SOLVD trial. One mechanism that could explain these clinical benefits is the beneficial effect of enalapril on left ventricular remodeling and diastolic properties (5). Furthermore, prevention of early nonfatal cardiac ischemic events by enalapril during in-trial treatment (3) may lead to a late benefit in mortality. The original SOLVD data showed that enalapril reduced the incidence of cardiac ischemic events. The present study extended this finding by showing that the risk of death or nonfatal cardiac ischemic events remained significantly lower in the early enalapril group than in the delayed group. This suggests that earlier treatment initiation may confer long-term protection against atherosclerotic complications by a sustained beneficial effect on plaque stability and vascular remodeling (3,6). Moreover, our data suggested that on the event-free patients, middle-aged asymptomatic subjects derived the most protection from early enalapril therapy. This observation confirms the need to initiate enalapril without delay in patients with reduced ejection fractions, even in the absence of symptoms. However, we could not exclude that genetic variations might also explain this excellent long-term evolution.

In conclusion, in the 15-year follow-up of the Belgian SOLVD cohort, early enalapril therapy prevented late deaths and serious CV morbid events beyond the original trial period. Our data also refuted the suggestion that ACE inhibitors in patients with asymptomatic or minimally symptomatic ventricular dysfunction would not confer any long-term benefit except for masking the development of heart failure. Our study showed the importance of starting ACE inhibitor therapy as early as possible in patients with left ventricular systolic dysfunction to avoid any delay resulting in any significant loss of benefits years later.

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doi:10.1016/j.jacc.2006.02.008

Please note: This study was supported in part by a research grant from Merck Frosst, Kirkland, Canada, and Merck Sharp and Dohme, Rahway, New Jersey.

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Short QT Interval and Atrial Fibrillation in Patients Without Structural Heart Disease

To the Editor: The short QT syndrome is a newly described clinical entity characterized by the presence of a short QT interval associated with cardiac tachyarrhythmias in otherwise healthy individuals. A genetic basis has been identified linking the disease to mutations in KCNH2 in the familial forms and a mutation in KCNQ1 in a sporadic form of the disease (1). The description of a novel, de novo gain of function mutation in KCNQ1, responsible for atrial fibrillation (AF) and short QT syndrome in utero, indicates that gain of function mutations in KCNQ1 channels can shorten the duration of both ventricular and atrial action potentials (2), which could account for the high incidence of AF in patients with short QT syndrome (3). Atrial fibrillation can occur in the